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(54) Title: CRYSTALLINE BASE OF CITALOPRAM

(57) Abstract: The present invention relates to the crystalline base of the well known antidepressant drug citalopram, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile, formulations of said base, a process for the preparation of purified salts of citalopram, such as the hydrobromide, using the base, the salts obtained by said process and formulations containing such salts.

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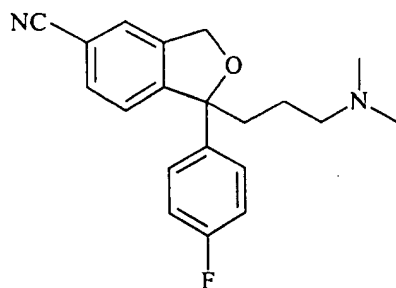
Crystalline Base of Citalopram

The present invention relates to the crystalline base of the well known antidepressant drug citalopram, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran-carbonitrile, formulations of said base, a process for the preparation of purified salts of citalopram, such as the hydrobromide, using the base, the salts obtained by said process and formulations containing such salts.

Background of the Invention

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Citalopram is a well-known antidepressant drug that has now been on the market for some years and has the following structure:



(I)

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It is a selective, centrally acting serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitor, accordingly having antidepressant activities. The antidepressant activity of the compound has been reported in several publications, eg. J. Hyttel, *Prog. Neuro-Psychopharmacol. & Biol. Psychiat.*, **1982**, 6, 277-295 and A. Gravem, *Acta Psychiatr. Scand.*, **1987**, 75, 478-486. The compound has further been disclosed to show effects in the treatment of dementia and cerebrovascular disorders, EP-A-474580.

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Citalopram was first disclosed in DE 2,657,013, corresponding to US 4,136,193. This patent publication describes the preparation of citalopram by one method and outlines a further method, which may be used for preparing citalopram. The citalopram prepared was isolated as the oxalate, the hydrobromide and the hydrochloride salt, respectively. Furthermore, the citalopram base was obtained as an oil (B.P. 175 C/0.03 mmHg). Citalopram is marketed as the hydrobromide and the hydrochloride, respectively.

25

A number of processes for the preparation of citalopram have been disclosed. In many of these, the last step of the process is a conversion of a group different from cyano in the 5 position of the direct analogue of citalopram to a 5-cyano group. So citalopram has been prepared by:

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Exchange of 5-halogen, or 5-CF₃-(CF₂)_n-SO₂-O- with cyano (DE 2,657,013 and co-pending WO 0011926 and WO 0013648)

Conversion of a 5-amido or 5-ester group to a 5-cyano group (WO 9819513)

5 Conversion of a 5-amino group to a 5-cyano group (WO 9819512)

Conversion of a 5-formyl group to a 5-cyano group (WO 9900548)

Conversion of a 5-oxazolinyl or 5-thiazolinyl group to a 5-cyano group (WO 0023431)

10 Other processes for the preparation of citalopram comprise exchange of the 5-bromo group of 1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuranbromide with 5-cyano followed by alkylation with a 3-(N,N-dimethylamino)propyl-halogenide (DE 2,657,013 and WO 9819511).

Many of the processes mentioned above have the disadvantage that it is difficult to separate the intermediates formed during the process (the intermediates mentioned above or earlier
15 intermediates) from the end product and, accordingly, extensive purification procedures involving loss of citalopram are required in order to obtain the necessary quality of the end product.

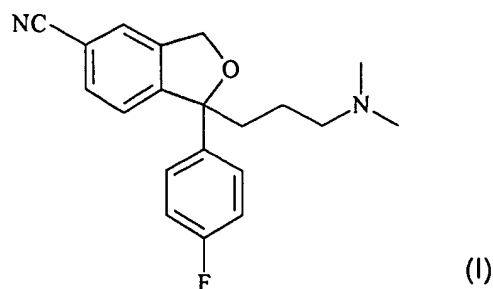
It has now been found that the base of citalopram may be obtained as a very nice and pure crystalline product, which may easily be handled and conveniently be formulated into tablets and other
20 pharmaceutical forms. Furthermore, it has surprisingly been found that a very good and efficient purification of citalopram may be obtained during manufacture of citalopram (e.g. of the hydrobromide or the hydrochloride salt) by crystallising the base, and thereafter optionally forming a salt from the base.

25 This purification process is particularly useful for removing intermediates which are structurally closely related to citalopram, in particular compounds which only differ from citalopram by the substituent situated in position 5 on the isobenzofurane ring, and intermediates which have physical/chemical properties which are close to those of citalopram, e.g. the 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-isobenzofuranes having halogen (in
30 particular bromide and chloride), an amide or an ester in position 5 of the isobenzofurane ring, or 1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuranbromide, or -chloride.

Summary of the invention

35 The present invention provides the crystalline base of the compound

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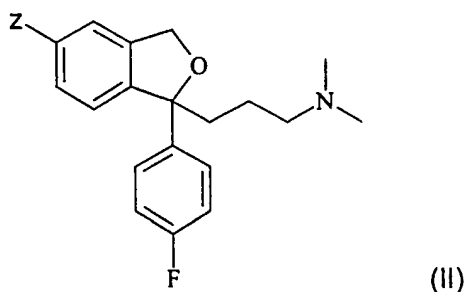
In a second aspect, the invention provides a process for the manufacture of a salt of citalopram, preferably the hydrobromide or hydrochloride in which the free base of citalopram is precipitated in crystalline form, optionally re-crystallised one or more times and then transferred to a pharmaceutically acceptable salt of citalopram.

In a further aspect, the invention relates to the pure crystalline salt, preferably the hydrobromide or hydrochloride prepared by the process of the invention.

In particular, the invention relates to a process for the manufacture of a salt of citalopram characterised in that the base of citalopram is set free and precipitated in crystalline form, optionally re-crystallised one or more times, and then transferred into a salt thereof.

In particular, the invention relates to a process for the manufacture of a salt of citalopram characterised in that the base of citalopram is set free from a crude salt or crude mixture of citalopram.

More particularly, the present invention relates to a process for the manufacture of citalopram base or a salt of citalopram characterised in that one or more impurities of the formula



wherein Z is halogen, $-O-SO_2-(CF_2)_n-CF_3$, where n is 0-8, $-CHO$, $-NHR^1$, $-COOR^2$, $-CONR^2R^3$ wherein R^2 and R^3 are selected from hydrogen, alkyl, optionally substituted aryl or aralkyl and R^1 is hydrogen or alkylcarbonyl, are removed from a crude mixture of citalopram or from a crude salt of

citalopram, by precipitating citalopram base in crystalline form, optionally re-crystallising said base one or more times and/or transferring said base into a salt thereof.

5 The crude mixture of citalopram containing the compound of formula II as an impurity may be prepared by subjecting a compound of formula II to a cyanide exchange reaction with a cyanide source, or by subjecting 1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuranhalogenide, in particular the bromide, to a cyanide exchange reaction followed by alkylation with a 3-(N,N-dimethylamino)propyl-halogenide.

10 In a particular embodiment of the invention, Z is halogen, in particular bromide or chloride.

In a particularly preferred embodiment of the invention, the salt prepared is the hydrobromide or hydrochloride salt of citalopram.

15 The crude salt may be any convenient salt, such as the hydrobromide, hydrochloride, sulphate, oxalate, phosphate, nitrate or any other convenient salt. Other salts are salts of organic acids.

In a preferred embodiment of the invention, the crude salt is the sulphate, the hydrobromide or the hydrochloride salt.

20

The invention also relates to a hydrochloride or hydrobromide salt of citalopram prepared by the processes of the invention. In particular, the invention relates to a hydrochloride or hydrobromide salt of citalopram having a purity of more than 99.8 %w/w, preferably more than 99.9 %w/w.

25 In yet another aspect, a pharmaceutical formulation of the free base of citalopram, or a hydrobromide or hydrochloride prepared from said base, is provided. Preferably the formulation is for oral administration.

30 The formulations according to the invention may be prepared by direct compression of citalopram in admixture with conventional adjuvants or diluents. Alternatively, a wet granulate or a melt granulate of citalopram, optionally in admixture with conventional adjuvants or diluents may be used for compression of tablets.

35 In particular, the pharmaceutical composition of the invention contains the racemic mixture of citalopram base, citalopram hydrochloride or citalopram hydrobromide.

The crystalline base of citalopram is preferably more than 99.8% w/w pure, most preferably more than 99.9% w/w pure (peak area). The melting point is preferably a range within 90 – 93 °C, most

preferably 91 - 92 °C (DSC; onset, open capsule) or it is between 92 and 94°C, preferably 92.5 and 93.5 °C (DSC; onset, closed capsule). The crystalline base of citalopram is preferably in racemic form.

- 5 The terms "crude salt" and "crude mixture" refer to the fact that the salt and the mixture, respectively, comprise impurities, in particular impurities of formula II, which must be removed or which it is desired to remove.

- The crude salt may be a salt separated directly from the reaction mixture, or the crude reaction
- 10 mixture may have been subjected to some initial purification, e.g. one re-crystallisation, and /or treatment with activated carbon or silica gel, and the salt formed subsequently by treatment with an acid using methods known in the art. The salt may be isolated by precipitation or it may exist in a solvent, e.g. in the mixture resulting directly from the synthesis of the salt.
- 15 Similarly, the crude mixture comprising citalopram may be obtained directly from the synthesis of the compound according to any of the above mentioned processes or it may have been subjected to some initial or simultaneous purification, e.g. one re-crystallisation, treatment with activated carbon or silica gel.
- 20 The base of citalopram may be set free from the crude salt by dissolving the crude salt in a mixture of water and an organic solvent and then adding a base. The organic solvent may be toluene, ethyl acetate or any other suitable solvent and the base may be any convenient base, preferably NaOH or NH₃. Likewise, the base of citalopram may, if necessary, be set free from a crude mixture containing citalopram by treatment with a base.

25

- Crude mixtures containing citalopram base may be subjected to further purification and extraction, before the base is precipitated in crystalline form. The base of citalopram may be isolated by separation of the organic phase, evaporation of the solvent in order to obtain the base most probably as an oil and then crystallisation of the base from an aprotic solvent, such as an alkane, including n-
- 30 heptane, hexane and isooctane, and high and low boiling petroleum ethers and substituted aromates, incl toluene and xylenes. Crystalline citalopram base may be re-crystallised from the same solvents.

- The pharmaceutically acceptable salt of citalopram, such as the hydrobromide or hydrochloride, may be prepared by methods known in the art. So, the base may be reacted with either the calculated
- 35 amount of acid in a water miscible solvent, such as acetone or ethanol, with subsequent isolation of the salt by concentration and cooling, or with an excess of the acid in a water immiscible solvent, such as ethylether, ethylacetate or dichloromethane, with the salt separating spontaneously. The

hydrobromide or hydrochloride of citalopram obtained by the method of the invention has a very high purity, preferably more than 99,8% pure, most preferably more than 99,9 % purity. Other salts of citalopram, e.g. the oxalate, may also be obtained in a very pure form by this process.

- 5 The cyanide exchange reactions mentioned above may be carried out as described in the patent applications mentioned above.

In particular, when Z is halogen, or $\text{CF}_3\text{-(CF}_2)_n\text{-SO}_2\text{-O-}$ wherein n is an integer in the range 0-8, incl., the conversion to a cyano group may be carried out by reaction with a cyanide source, for
 10 example KCN, NaCN, CuCN, Zn(CN)_2 or $(\text{R}^4)_4\text{NCN}$ where R^4 indicates four groups which may be the same or different and are selected from hydrogen and straight chain or branched alkyl, in the presence of a palladium catalyst and a catalytic amount of Cu^+ or Zn^{2+} , or with Zn(CN)_2 in the presence of a palladium catalyst.

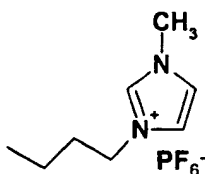
- 15 The cyanide source is used in a stoichiometric amount or in excess, preferably 1-2 equivalents are used pr. equivalent starting material. R^4N^+ may conveniently be $(\text{Bu})_4\text{N}^+$. The cyanide compound is preferably NaCN or KCN or Zn(CN)_2 .

The palladium catalyst may be any suitable Pd(0) or Pd(II) containing catalyst, such as $\text{Pd(PPh}_3)_4$,
 20 $\text{Pd}_2(\text{dba})_3$, $\text{Pd(PPh)}_2\text{Cl}_2$, etc. The Pd catalyst is conveniently used in an amount of 1-10, preferably 2-6, most preferably about 4-5 mol%.

Catalytic amounts of Cu^+ and Zn^{2+} , respectively, means substoichiometric amounts such as 0.1 - 5, preferably 1 - 3 %. Conveniently, about $\frac{1}{2}$ eq. is used per eq. Pd. Any convenient source of Cu^+
 25 and Zn^{2+} may be used. Cu^+ is preferably used in the form of CuI and Zn^{2+} is conveniently used as the Zn(CN)_2 salt.

When Z is Br or I, the conversion to a cyano group may also be carried out by reaction with Cu(CN) without catalyst. In a preferred embodiment, the reaction is performed at elevated temperature.
 30

In another aspect of the invention, the reaction is performed in an ionic liquid of the general formula $(\text{R}^5)_4\text{N}^+$, X^- , wherein R^5 are alkyl-groups or two of the R^5 groups together form a ring and X^- is the counterion. In one embodiment of the invention, $(\text{R}^5)_4\text{N}^+\text{X}^-$ represents



In another particular aspect, the reaction is conducted with apolar solvents such as benzene, xylene or mesitylene and under the influence of microwaves by using *i.e.* Synthewave 1000™ by Prolabo. In a particular aspect, the reaction is performed without added solvent.

5

The temperature ranges are dependent upon the reaction type. If no catalyst is present, preferred temperatures are in the range of 100-200°C. However, when the reaction is conducted under the influence of microwaves, the temperature in the reaction mixture may raise to above 300 °C. More preferred temperature ranges are between 120-170°C. The most preferred range is 130-150°C.

- 10 If catalyst is present, the preferred temperature range is between 0 and 100°C. More preferred are temperature ranges of 40-90°C. Most preferred temperature ranges are between 60-90°C.

Other reaction conditions, solvents, etc. are conventional conditions for such reactions and may easily be determined by a person skilled in the art.

15

When Z is Cl or Br, the conversion to a cyano group may also be carried out by reaction with a cyanide source, for example KCN, NaCN, CuCN, Zn(CN)₂ or (R⁴)₄NCN where (R⁴)₄ indicates four groups which may be the same or different and are selected from hydrogen and straight chain or branched alkyl, in the presence of a nickel catalyst.

20

The nickel catalyst may be any suitable Ni(0) or Ni(II) containing complex which acts as a catalyst, such as Ni(PPh₃)₃, (σ-aryl)-Ni(PPh₃)₂Cl, etc. The nickel catalysts and their preparation are described in WO 96/11906, EP-A-613720 or EP-A-384392.

- 25 In one embodiment of the invention, the reaction is carried out in the presence of a catalytic amount of Cu⁺ or Zn²⁺.

In a particularly preferred embodiment, a Nickel(0) complex is prepared *in situ* before the cyanation reaction by reduction of a Nickel(II) precursor such as NiCl₂ or NiBr₂ by a metal, such as zinc, magnesium or mangan in the presence of excess of complex ligands, preferably triphenylphosphin.

30

The Ni-catalyst is conveniently used in an amount of 0.5-10, preferably 2-6, most preferably about 4-5 mol%.

Catalytic amounts of Cu^+ and Zn^{2+} , respectively, mean substoichiometric amounts such as 0.1 - 5, preferably 1 - 3 %. Any convenient source of Cu^+ and Zn^{2+} may be used. Cu^+ is preferably used in the form of CuI and Zn^{2+} is conveniently used as the $\text{Zn}(\text{CN})_2$ salt or formed in situ by reduction of a Nickel (II) compounds using zinc.

5

The Ni catalysts are *i.e.* Ni (0), Pd(0) or Pd(II) catalysts as described by Sakakibara et. al. in Bull. Chem. Soc. Jpn., 61, 1985-1990, (1988). Preferred catalysts are $\text{Ni}(\text{PPh}_3)_3$ or $\text{Pd}(\text{PPh}_3)_4$, or $\text{Pd}(\text{PPh})_2\text{Cl}_2$.

- 10 The reactions may be performed in any convenient solvent as described in Sakakibara et. al. in Bull. Chem. Soc. Jpn., 61, 1985-1990, (1988). Preferred solvents are acetonitril, ethylacetat, THF, DMF or NMP.

- 15 When Z is CHO, the conversion to a cyano group may be carried out by conversion of the formyl group to an oxime or similar group by reaction with a reagent $\text{R}^6\text{-V-NH}_2$ wherein R^6 is hydrogen, optionally substituted alkyl, aryl or heteroaryl and V is O, N or S, followed by dehydration with a common dehydrating agent, for example thionylchloride, acetic anhydride/pyridine, pyridine/HCl or phosphor pentachloride. Preferred reagents $\text{R}^6\text{-V-NH}_2$ are hydroxylamin and compounds wherein R^6 is alkyl or aryl and V is N or O.

20

When Z is $-\text{COOH}$, the conversion to a cyano group may be carried out via the corresponding acid chloride, ester or amide.

- 25 The acid chloride is conveniently obtained by treatment of the acid with POCl_3 , PCl_5 or SOCl_2 neat or in a suitable solvent, such as toluene or toluene comprising a catalytic amount of N,N-dimethylformamide. The ester is obtained by treatment of the acid with an alcohol, in the presence of an acid, preferably a mineral acid or a Lewis acid, such as HCl, H_2SO_4 , POCl_3 , PCl_5 or SOCl_2 . Alternatively, the ester may be obtained from the acid chloride by reaction with an alcohol. The ester or the acid chloride is then converted to an amide or by amidation with ammonia or an alkylamine, 30 preferably t-butyl amine.

The conversion to amide may also be obtained by reaction of the ester with ammonia or an alkylamine under pressure and heating.

- 35 The amide group is then converted to a cyano group by dehydration. The dehydrating agent may be any suitable dehydrating agent, and the optimal agent may easily be determined by a person skilled in the art. Examples of suitable dehydrating agents are SOCl_2 , POCl_3 and PCl_5 , preferably SOCl_2 .

In a particularly preferred embodiment, the carboxylic acid is reacted with an alcohol, preferably ethanol, in the presence of POCl_3 , in order to obtain the corresponding ester, which is then reacted with ammonia thereby giving the corresponding amide, which in turn is reacted with SOCl_2 in
5 toluene comprising a catalytic amount of N,N-dimethylformamide.

Alternatively, a compound where Z is $-\text{COOH}$ may be reacted with chlorosulfonyl isocyanate in order to form the nitrile, or treated with a dehydrating agent and a sulfonamide.

10 When Z is $-\text{NHR}^1$, where R^1 is hydrogen, the conversion into cyano is preferably performed by diazotation and followed by reaction with CN^- . Most preferably NaNO_2 and CuCN and/or NaCN are used. When R^1 is alkylcarbonyl, it is initially subjected to hydrolysis thereby obtaining the corresponding compound wherein R^1 is H which is then converted as described above. The hydrolysis may be performed either in acidic or basic environment.

15

The compounds of formula (II) may be prepared as described in DE 2,657,013, WO 0011926 and WO 0013648, WO 9819513, WO 9819512 and WO 9900548.

Throughout this specification with claims halogen means chloro, bromo or iodo.

20

The term alkyl refers to a branched or unbranched alkyl group, such as methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl, and 2-methyl-1-propyl.

The term aryl refers to a carbocyclic aromatic group, in particular phenyl. Aralkyl refers to an
25 arylalkyl group wherein aryl and alkyl is as defined above. The aryl and aralkyl groups may optionally be substituted, e.g. with alkyl groups, forming for example tolyl.

The pharmaceutical compositions of the invention may be administered in any suitable way and in any suitable form, for example orally in the form of tablets, capsules, powders or syrups, or
30 parenterally in the form of usual sterile solutions for injection. Preferably the pharmaceutical compositions of the invention are administered orally.

The pharmaceutical formulations of the invention may be prepared by conventional methods in the art. For example, tablets may be prepared by mixing the active ingredient with ordinary adjuvants
35 and/or diluents and subsequently compressing the mixture in a conventional tableting machine. Examples of adjuvants or diluents comprise: Corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvant or additive colourings, aroma, preservatives etc. may be used provided that they are compatible with the active ingredients.

In particular, the formulations according to the invention may be prepared by direct compression of citalopram in admixture with conventional adjuvants or diluents. Alternatively, a wet granulate or a melt granulate of citalopram, optionally in admixture with conventional adjuvants or diluents may be used for compression of tablets.

Solutions for injections may be prepared by solving the active ingredient and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to the desired volume, sterilisation of the solution and filling in suitable ampoules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, etc.

According to the present invention, the base of citalopram has been found to be crystalline with stable and nice white crystals and it has been found that the base may easily be crystallised in a very pure form. So for example more than 99.8% w/w pure citalopram base was obtained by crystallisation from up to 95% pure hydrobromide without further purification. Accordingly, the process of the invention for preparing salts of citalopram has been found to give the salts as very pure products of pharmaceutically acceptable quality. Accordingly, the yield may be improved substantially during the manufacture of citalopram.

Finally, it has been found that the crystalline citalopram base may be formulated into very good and stable solid formulations with good release properties.

The invention is further illustrated by the following examples.

Example 1

25 Crystallisation of R,S-Citalopram as the free base.

1-(3-Dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydrobenzofuran-5-carbonitrile.

1-(3-Dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydrobenzofuran-5-carbonitrile hydrobromide (101 grams, 0.25 mole) prepared from 1-(3-Dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydro-5-isobenzofuranbromide, is suspended in water (500 ml) and toluene (500 ml). NaOH (60 ml, 5 N (aq)) is added and the mixture (pH>10) is stirred for 15 min. before the phases are separated. The organic phase is washed with water (2x100 ml) and filtered through a pad of filter help. The volatiles are removed *in vacuo* and the title compound is obtained as an oil. n-Heptane (400 ml) is added and the mixture is heated to 70 °C. On cooling, crystals form. The white crystals of the title compound are filtered off and dried at ambient temperature over night in *vacuo*. Yield: 75.4 grams (93%). DSC(onset, open capsule): 91.3-91.8 °C DSC (onset, closed capsule): 92.8 °C. Purity: (> 99.8 % (peak area)).

Anal. calcd. for C₂₀H₂₁N₂F₁₀O₁; C, 74.04; H, 6.54; N, 8.64. Found C, 74.01; H, 6.49; N, 8.59.

¹H-NMR (DMSO-d₆, 500 MHz): 1.21 (1H, m), 1.29 (1H, m), 2.02 (6H, s), 2.09-2.23 (4 H, m), 5.15 (1H, d J=12.5 Hz), 5.22 (1H, d J=12.5 Hz), 7.16 (2H, t J=8.5 Hz), 7.60 (2H, dt J=8.5 Hz J=1.2 Hz), 7.76 (1H, d J= 8.5 Hz), 7.79 (1H, d J=8.5 Hz), 7.80 (1H, s). ¹³C-NMR (DMSO-d₆, 125 MHz):

21.8, 38.3, 45.0, 58.8, 71.0, 90.7, 110.5, 115.1 (d J=22 Hz), 118.8, 123.1, 125.1, 127.0 (d J=8 Hz), 132.0, 140.0 (d J=3 Hz), 140.5, 149.5, 161.3 (d J=245Hz).

Example 2

- 10 a) A crude mixture of Citalopram and sulphuric acid is made basic by adding NaOH and the citalopram base is extracted with toluene. The toluene is evaporated and the citalopram base obtained is dissolved in n-heptane at elevated temperature. The very pure free base of citalopram is precipitated by cooling.
- 15 b) A crude mixture of Citalopram and sulphuric acid is made basic by adding NaOH and the citalopram base is extracted with toluene. The toluene is evaporated and the citalopram base obtained is dissolved in methanol. The mixture is treated with activated carbon and filtrated and the solvent is evaporated. The purified free base is dissolved in n-heptane at elevated temperature. Then the very pure free base of citalopram is precipitated by cooling.
- 20 c) A crude mixture of Citalopram and sulphuric acid is made basic by adding NaOH and the citalopram base is extracted with toluene. The toluene phase is treated with silicagel, the toluene is evaporated and the citalopram base obtained is dissolved in n-heptane at elevated temperature. The very pure free base of citalopram is precipitated by cooling.
- 25 d) A crude mixture of Citalopram and sulphuric acid is made basic by adding NaOH and the citalopram base is extracted with toluene. The toluene phase is treated with silicagel, the toluene is evaporated and the citalopram base obtained is dissolved in methanol. The mixture is treated with activated carbon and filtrated and the solvent is evaporated. The purified free base is dissolved in n-
- 30 heptane at elevated temperature. Then the extremely pure free base of citalopram is precipitated by cooling.

Example 3

Wet granulation and preparation of tablets

35

The batch size was 200 g and the granulation was performed in a small-scale laboratory high shear mixer (Micromixer).

Citalopram base was sieved through a sieve aperture of 0.3 mm. The ingredients of the intragranular phase (1 - 4 in Table 1) were mixed at 600 rpm. 25 ml of purified water (5) was added in 30 sec and the granulation terminated after a total processing time of 3 min. The granulate was wet sieved through a 0.7 mm sieve aperture and dried at 40 °C in 30 minutes to equilibrium relative humidity of 32 %. The dried granulate was finally sieved through a 0.7 mm sieve aperture.

The dried granulate was mixed for 3 minutes with the extragranular phase (6 – 7) in a Turbula mixer and finally mixed with the lubricant (8) for 30 sec.

10

	Materials	%
1	Citalopram (base)	16.00
2	Kollidon VA64	2.32
3	Lactose 350 mesh	38.98
4	Corn starch	20.00
5	Purified water	25
6	Avicel PH 200 (Microcrystalline cellulose)	20.00
7	Ac-Di-Sol (Croscarmellose sodium)	2.00
8	Magnesium stearate	0.7

Table 1. Composition of the tablets.

Tablets were produced on a single punch tableting machine Korsch EK0. The characteristics of the tables are shown in Table 2.

15

Parameter	Values
Tablet strength, mg	20
Nominal tablet weight, mg	125
Tablet diameter, mm	7
Tablet shape	Film coating (special doomed)
Mean disintegration time, min	1.77
Mean chrushing strength, N	69.1
Mean tablet weight, mg	125.4
RSD tablet weight, %	0.42
Friability, %	0.3

Table 2. Tablet characteristics.

The tablets produced had satisfactory technical properties.

Example 4**Melt granulation**

- 5 The batch size was 200 g. Citalopram base was sieved through a sieve aperture of 0.3 mm. The granulation was performed in a small-scale laboratory high shear mixer (Micromixer)

The ingredients of the intra-granular phase (1 - 3 in Table 3) were mixed at 1200 rpm.

- The jacket temperature was 80 °C. The granulation process was terminated after 3.5 min. The
 10 granulate was sieved through a sieve aperture of 1.0 mm and mixed with the extra-granular phase (4, 5) for 3 min. and with the lubricant (6) for 30 sec.

	Materials	%
1	Citalopram (base)	16.00
2	Polyethyleneglycol 6000	9.14
3	Lactose 350 mesh	38.98
4	Avicel PH 200 (Microcrystalline cellulose)	30.00
5	Kollidon CL (Cross-linked povidone)	4.00
6	Magnesium stearate	0.7

Table 3. Composition of the tablet.

- 15 Tablets were produced on a single punch tableting machine Korsch EK0. The characteristics of the tables are shown in Table 4.

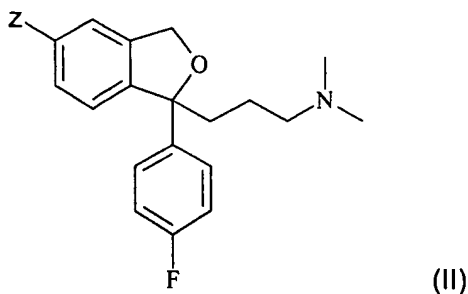
Parameter	Values
Tablet strength, 20 mg	20
Nominal tablet weight, mg	125
Tablet diameter, mm	7
Tablet shape	Film coating , Special doomed
Mean disintegration time, min	1.0
Mean crushing strength, N	55.5
Mean tablet weight, mg	125.6
RSD tablet weight, %	0.5
Friability, %	0.4

Table 4. Tablet characteristics.

- 20 The tablets produced had satisfactory technical properties.

CLAIMS

1. A process for the manufacture of a salt of citalopram characterised in that the base of citalopram is set free and precipitated in crystalline form, optionally re-crystallised one or more times, and then transferred into a salt thereof.
2. The process of Claim 1 for the manufacture of a salt of citalopram characterised in that the base of citalopram is set free from a crude salt or a crude mixture of citalopram.
3. A process for the manufacture of citalopram base or a salt of citalopram characterised in that one or more impurities of the formula



- wherein Z is halogen, $-O-SO_2-(CF_2)_n-CF_3$, where n is 0-8, $-CHO$, $-NHR^1$, $-COOR^2$, $-CONR^2R^3$ wherein R^2 and R^3 are selected from hydrogen, alkyl, optionally substituted aryl or aralkyl and R^1 is hydrogen or alkylcarbonyl, are removed from a crude mixture of citalopram or from a crude salt of citalopram, by precipitating citalopram base in crystalline form, optionally re-crystallising said base one or more times and/or transferring said base into a salt thereof.
4. The process according to Claim 3 wherein the crude mixture of citalopram containing the compound of formula II as an impurity, is prepared by subjecting a compound of formula II to a cyanide exchange reaction with a cyanide source.
5. The process according to Claim 3, wherein Z is halogen, in particular bromide or chloride.
6. The process according to Claims 3 to 5 wherein the crude mixture of citalopram is subjected to initial purification before the base of citalopram is precipitated in crystalline form.
7. The process according to Claims 3 to 5 wherein the crude mixture of citalopram is subjected to initial purification before a crude salt is formed from said crude mixture.

8. The process according to Claims 3 to 7 wherein the base of citalopram is set free from a crude salt or a crude mixture of citalopram by treatment with a base and optionally subjected to further purification before the base of citalopram is precipitated in crystalline form.
- 5 9. The process according to any of Claims 1 to 8 characterised in that the citalopram base is transferred into the hydrobromide or the hydrochloride salt of citalopram.
- 10 10. The process according to any of Claims 2-3, characterised in that the crude salt is a hydrobromide, hydrochloride, sulphate, oxalate, phosphate or nitrate salt, preferably the sulphate hydrobromide, or hydrochloride salt.
11. A crystalline base of citalopram, or a hydrochloride or hydrobromide salt of citalopram, characterised in that it has a purity of more than 99.8 %w/w, preferably more than 99.9 %w/w.
- 15 12. The crystalline base of citalopram, or a hydrochloride or hydrobromide salt of citalopram prepared by the process of any of Claims 1-10.
13. The base, the hydrochloride or the hydrobromide salt of claim 12 characterised in that it has a purity of more than 99.8 %w/w, preferably more than 99.9 %w/w.
- 20 14. A pharmaceutical composition containing the hydrochloride or the hydrobromide salt of citalopram according to Claims 11 to 13, or the crystalline base of citalopram.
15. A pharmaceutical composition according to Claim 14 which is a tablet prepared by
- 25 a) direct compression of citalopram, optionally in admixture with pharmaceutically acceptable adjuvants;
- b) by compression of a wet granulate of the citalopram, optionally in admixture with pharmaceutically acceptable adjuvants; or
- c) by compression of a melt granulate of the citalopram, optionally in admixture with
- 30 pharmaceutically acceptable adjuvants.
16. The pharmaceutical composition according to Claims 14 to 15 characterized in that it contains the racemic mixture of citalopram base, citalopram hydrochloride or citalopram hydrobromide.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 01/00137

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 307/87

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0347066 A1 (H. LUNDBECK A/S), 20 December 1989 (20.12.89), example 3 --	1-16
A	DE 2657013 A1 (KEFALAS A/S), 28 July 1977 (28.07.77)	3-10
X	--	11-16
A	WO 0011926 A2 (H. LUNDBECK A/S), 9 March 2000 (09.03.00)	3-10
X	-- -----	11-16

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT
Information on patent family members

02/04/01

International application No.

PCT/DK 01/00137

Patent document cited in search report			Publication date	Patent family member(s)	Publication date
EP	0347066	A1	20/12/89	SE 0347066 T3	
				AT 119896 T	15/04/95
				AU 623144 B	07/05/92
				AU 3629589 A	04/01/90
				CA 1339568 A	02/12/97
				CY 2081 A	16/10/98
				DE 68921672 D,T	27/07/95
				DK 11593 A	01/02/93
				DK 170280 B	24/07/95
				DK 259989 A	15/12/89
				ES 2068891 T	01/05/95
				FI 91527 B,C	31/03/94
				FI 98627 B,C	15/04/97
				FI 892823 A	15/12/89
				FI 941829 A	20/04/94
				FI 20000507 A	06/03/00
				GB 8814057 D	00/00/00
				GR 3015889 T	31/07/95
				HK 139596 A	02/08/96
				HU 211460 B	28/11/95
				HU 9500496 A	28/09/95
				IE 65734 B	15/11/95
				IL 90465 A	24/01/95
				JP 2036177 A	06/02/90
				JP 3038204 B	08/05/00
				JP 3044253 B	22/05/00
				JP 11292867 A	26/10/99
				MX 9203346 A	31/08/92
				NO 172892 B,C	14/06/93
				NO 892447 A	15/12/89
				NZ 229426 A	21/12/90
				PT 90845 A,B	29/12/89
				US RE34712 E	30/08/94
				US 4943590 A	24/07/90
				ZA 8904476 A	25/04/90

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

02/04/01

PCT/DK 01/00137

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
DE	2657013	A1	28/07/77	AT	359488 B	10/11/80
				AT	360001 B	10/12/80
				AT	360002 B	10/12/80
				AT	571979 A	15/05/80
				AT	572079 A	15/05/80
				AT	947276 A	15/04/80
				AU	509445 B	15/05/80
				AU	2107377 A	13/07/78
				BE	850401 A	14/07/77
				CA	1094087 A	20/01/81
				CH	626886 A	15/12/81
				CH	632258 A	30/09/82
				CH	632259 A	30/09/82
				DK	13177 A	15/07/77
				DK	143275 B,C	03/08/81
				ES	454980 A	01/04/78
				FI	63754 B,C	29/04/83
				FI	770073 A	15/07/77
				FR	2338271 A,B	12/08/77
				GB	1526331 A	27/09/78
				IE	44055 B	29/07/81
				JP	1368581 C	11/03/87
				JP	52105162 A	03/09/77
				JP	61035986 B	15/08/86
				NL	192451 B,C	01/04/97
				NL	7700244 A	18/07/77
				NO	147243 B,C	22/11/82
				NO	770109 A	15/07/77
				NZ	183001 A	02/06/78
				SE	429551 B,C	12/09/83
				SE	7614201 A	15/07/77
				US	4136193 A	23/01/79
				ZA	7700057 A	30/11/77
WO	0011926	A2	09/03/00	AU	1374800 A	21/03/00
				FI	20010154 A	09/02/01
				GB	0101508 D	00/00/00
				GB	2354240 A	21/03/01
				IT	MI991579 D	00/00/00
				NO	20010318 A	20/02/01
				SE	0100194 D	00/00/00